28 Dietary Fatty Acids and Eicosanoids

Joo Y. Lee and Daniel H. Hwang

CONTENTS

I. INTRODUCTION

One of the important functions of dietary fat is to provide essential fatty acids (EFAs). However, the requirement for EFAs as linoleic acid (18:2n-6) is only 1%–2% of the total caloric intake. Thus, EFA deficiency seldom occurs in the general population consuming ordinary diets. In spite of this, much greater amounts of intake for dietary polyunsaturated fatty acids (PUFAs) are generally recommended. This recommendation is primarily based on the cholesterol-lowering action of dietary PUFAs, and this, in part, resulted in changes in trends in the consumption of dietary fat in the United States (Stephen and Wald, 1990).

Dietary PUFAs has been generally used as an entity without differentiating the type of PUFA. Epidemiological, clinical, and biochemical studies conducted during the past 20 years suggest that dietary n-3 PUFA is beneficial in reducing certain risks of chronic diseases. Revelation of the difference existing between n-6 and n-3 fatty acids in metabolic pathways leading to the formation of eicosanoids and their precursor acids suggests that not only the level of PUFAs but also the types of PUFAs need to be defined for recommendation of dietary PUFAs in dietary guidelines in the future.

In this chapter, discussion is focused on how different dietary fatty acids affect the capacity of tissues to synthesize eicosanoids with diverse physiological actions and their nutritional implications.

II. DIETARY PUFAs AS A SOURCE OF ESSENTIAL FATTY ACIDS

In 1929, Burr and Burr first reported the essentiality of dietary fat (Burr and Burr, 1929). Later, it became clear that the essentiality of dietary fat is due to the requirement of linoleic acid (18:2n-6) and α-linolenic acid (18:3n-3), which cannot be synthesized by mammals. The requirement for linoleic acid is known to be only 1%–2% of the total daily caloric intake (Holman, 1970). This requirement is based on the amounts of linoleic acid that can clear the dermal lesion resulting from EFA deficiency or the amounts that normalize the triene/tetraene ratio (Mohrhauer and Holman, 1963). Ordinary American diets can provide linoleic acid at amounts much higher than required. Thus, EFA deficiency (based on overt symptoms and an increased triene/tetraene ratio) rarely occurs in the general population. However, it should be noted that the amount of EFAs required to prevent the deficiency symptoms may not represent the amount needed for optimal functioning of the body.

The major PUFAs in our diets are the n-6 fatty acids including linoleic acid, which is the predominant PUFA in most edible vegetable oils consumed in the United States. The major vegetable oils consumed in the United States are soybean, corn, and cottonseed oils, which comprise more than 82% of the total fats and oils used in foods (ISEO, 1988). More than 50% of the total fatty acids of these vegetable oils are linoleic acid.

Although a wide range of symptoms was ascribed to the deficiency of EFAs, their biological functions were unknown until early 1964, when Van et al. (1964) and Bergstroem et al. (1964) demonstrated that prostaglandins (PGs) are synthesized from PUFAs derived from dietary EFAs in animal tissues. It is now generally recognized that EFAs have both a structural role in maintaining the integrity of cell membranes and a functional role in serving as precursors of eicosanoids.

III. DIETARY ESSENTIAL FATTY ACIDS AS PRECURSORS OF EICOSANOIDS

Long-chain PUFAs, which are the precursors of eicosanoids, can be generated by the desaturation and elongation of dietary fatty acids in tissues, as shown in Figure 28.1.

Oleic acid (18:1n-9), which is the most abundant fatty acid in our food system, can be converted to 20:3n-9. This fatty acid cannot serve as a substrate for cyclooxygenase (COX). Therefore, no PGs is synthesized from 20:3n-9. However, 20:3n-9 is a substrate for 5-lipoxygenase (5-LOX) from rat RBL-1 cells leading to the formation of leukotriene A_3 (LTA_3) (Stenson et al., 1984).

There is an indication that 20:3n-7 derived from palmitoleic acid can be converted to PGs (Lands et al., 1977). However, 20:3n-7 does not accumulate in animal tissues in significant amounts. It has been shown that the 5- LOX in RBL-1 cells requires double bonds at C-5 and C-8 for catalysis to occur. This structural requirement suggests that 20:3n-7 is not a substrate for 5-LOX (Jakschik et al., 1980).

Linoleic acid (18:2n-6) can be desaturated and elongated to arachidonic acid (20:4n-6) in animal tissues. Arachidonic acid is the predominant 20-carbon PUFA present in most tissues of terrestrial animals. Thus, eicosanoids synthesized in animal tissues are mostly derived from arachidonic acid. The metabolic map for the arachidonic acid cascade is shown in Figure 28.2. Arachidonic acid is a precursor of "2-series" PGs and thromboxanes and 4-series leukotrienes. The biosynthesis and physiological actions of various eicosanoids have been reviewed extensively (Nicosia and Patrono, 1989; Samuelsson, 1983; Samuelsson et al., 1987; Smith et al., 1991).

α-Linolenic acid (18:3n-3) can be converted to longer-chain n-3 PUFAs by the same desaturases used for n-6 or n-9 fatty acids. The extent to which α-linolenic acid is converted to longer-chain PUFAs is not known. Dyerberg et al. (1980) suggested that α-linolenic acid is not converted to 20:5n-3 in humans on the basis of their observations that insignificant amounts of 20:5n-3 in plasma lipids were found in human subjects who consumed linseed oil. Similarly, Adam et al. (1986) showed

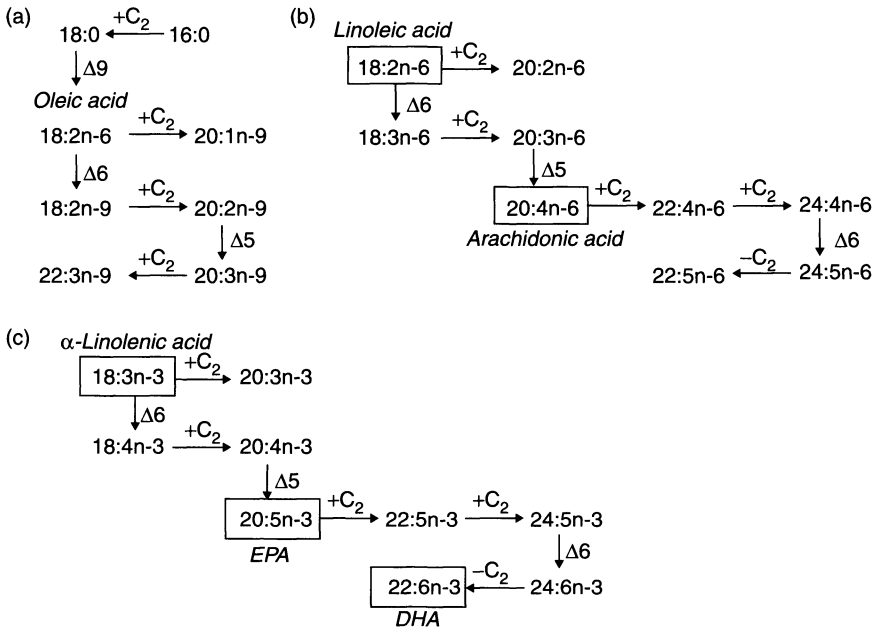

FIGURE 28.1 Conversion of dietary fatty acids to longer-chain polyunsaturated fatty acids and precursor acids for eicosanoids. The first number denotes the number of carbon atoms, the number after the colon denotes the number of double bonds, and the number after n denotes the position of the last double bond from the methyl end of fatty acids. EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid.

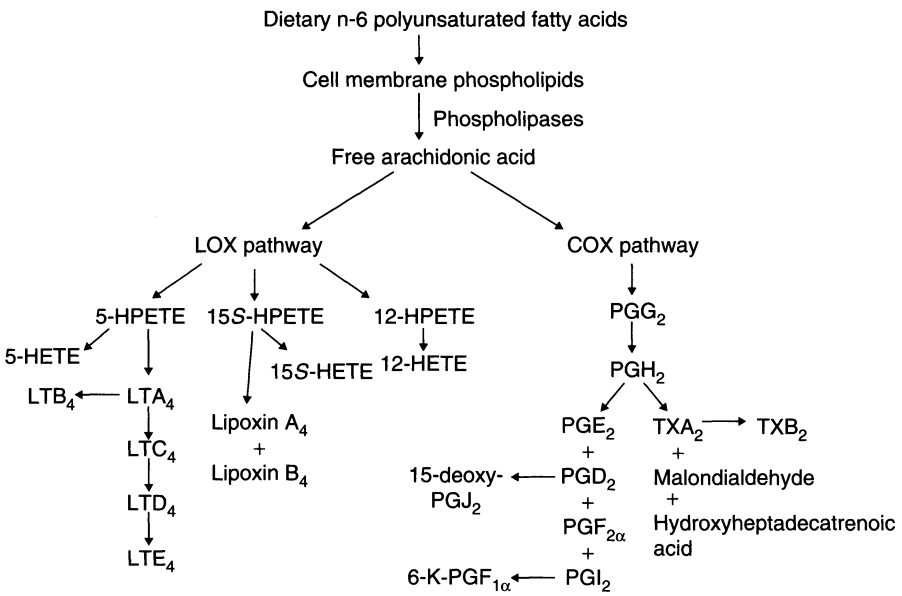

FIGURE 28.2 Eicosanoid formation from arachidonic acid via the cyclooxygenase and lipoxygenase pathways. LOX, lipoxygenase; COX-2, cyclooxygenase; LTA_4, leukotriene A_4; TXA_2, thromboxane A_2; PGH_2, prostaglandin H_2; HPETE, hydroperoxyeicosatetraenoic acid; HETE, hydroxyeicosatetraenoic acid.

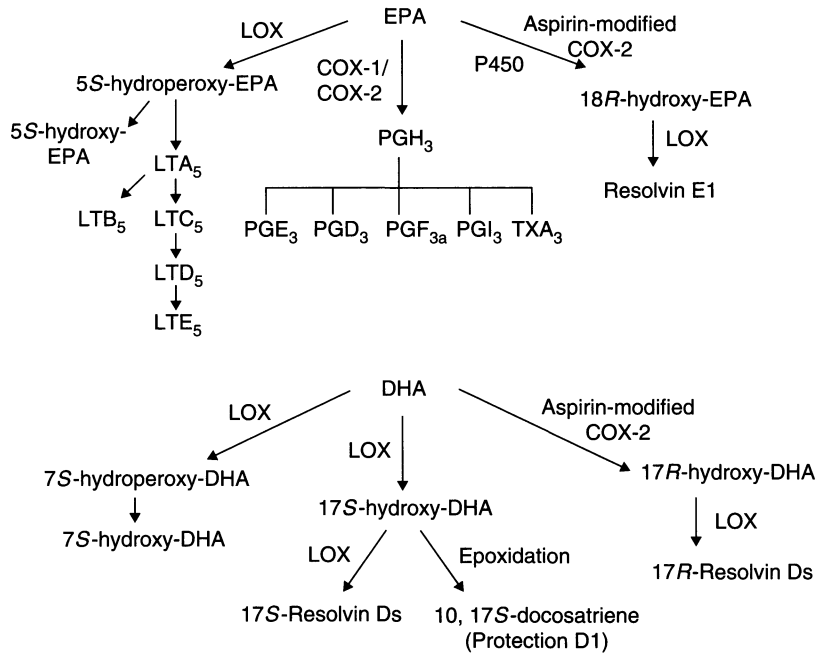

FIGURE 28.3 The biosynthesis of prostanoids, resolvins, and protectins from eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). The metabolism of EPA by cyclooxygenase (COX) leads to the formation of the "3-series" of prostanoids. The acetylated COX-2 by aspirin produces 18*R*-hydroxy-EPA in endothelial cells that are sequentially metabolized to Resolvin E1 by LOX in neutrophils.

that ingestion of α-linolenic acid did not affect levels of 18:3n-6 or 20:4n-6 in plasma and platelet phospholipids in human volunteers. However, levels of PGE_2 in urine samples were reduced by dietary α-linolenic acid in a dose-dependent fashion. Thus, the possibility that dietary α-linolenic acid can be desaturated and elongated to longer-chain n-3 fatty acids in other tissues cannot be ruled out on the basis of fatty acid composition of plasma and platelet lipids alone. Furthermore, the results of these studies were derived from relatively short-term feeding trials (less than 2 weeks).

Eicosapentaenoic acid (EPA, 20:5n-3) can be metabolized by both COX and 5-LOX leading to the formation of "3-series" PGs, thromboxane A_3 (TXA_3), and "5-series" leukotrienes (Figure 28.3) (Dyerberg et al., 1978; Fischer and Weber, 1983; Gryglewski et al., 1979; Needleman et al., 1979). EPA is a poorer substrate for COX than arachidonic acid (Culp et al., 1979). Thus, it acts as a competitive inhibitor. Since EPA is a poor substrate, tissues of animals fed fish oil diets synthesized *in vitro* very small amounts of triene PGs and TXA_3. However, it has been shown that urine samples of human subjects consuming fish oil contain greater amounts of metabolites of triene PGs than those of diene PGs derived from arachidonic acid (Fischer and Weber, 1983; FitzGerald et al., 1984). The reason for the discrepancy between the *in vivo* and *in vitro* results has not been resolved. Overall, these studies appear to have established the cause and effect relationships among dietary fatty acids, eicosanoid formation, their cellular responses, and perhaps certain chronic diseases. Aspirin-treated COX-2 converts EPA to 18*R*-hydroxy-EPA (18-HEPE) in vascular endothelial cells, which is further metabolized to resolvin E1 (5*S*,12*R*,18*R*-trihydroxy-6Z,8E,10E,14Z,16E-EPA) by 5-LOX in neutrophils (Serhan et al., 2000). EPA was shown to be a preferred substrate for 5-LOX as compared to arachidonic acid (Ochi et al., 1983). Thus, increasing dietary n-3 PUFAs suppressed LTB_4 formation and increased formation of LTB_5 in human neutrophils.

Docosahexaenoic acid (DHA, 22:6n-3) can be converted to 7*S*- or 17*S*-hydroperoxy-DHA by LOX. 17*S*-hydroxyDHA is further metabolized to 17*S*-Resolvin D by LOX or converted to 10,

TABLE 28.1
Physiological Actions of Eicosanoids

Eicosanoid	Effect
PGE_1	Inhibits platelet aggregation
PGE_2	Vasodilation; increases cAMP levels; decreases gastric acid secretion; suppresses immune response; luteotropic action
PGI_2	Relaxes smooth muscle; vasodilation; inhibits platelet aggregation; raises cAMP levels
TXA_2	Contracts smooth muscle; causes platelet aggregation; bronchoconstriction
PGD_2	Inhibits platelet aggregation; raises cAMP levels; causes peripheral vasodilation
LTB_4	Neutrophil and eosinophil chemotaxis; leakage in micro circulation; raises cAMP levels; causes neutrophil aggregation
LTC_4–LTD_4	Contracts smooth muscle; constricts peripheral airways; leakage in microcirculation; decreases cAMP levels
12-HETE–12-HPETE	Neutrophil chemotaxis; stimulates glucose-induced insulin secretion
15-HETE	Inhibits 5- and 12-lipoxygenases
Lipoxin A	Superoxide anion generation; chemotaxis; activates protein cell activity
Lipoxin B	Inhibits NK cell activity
Resolvins	Block PMN transmigration and infiltration; inhibit microglial cell cytokine expression
Protectins	Block PMN recruitment and activation; inhibit TNF-α secretion

Abbreviations: PG, prostaglandin; TX, thromboxane; LT, leukotrine; HETE, hydroxyeicosatetraenoic acid; HPETE, hydroperoxyeicosatetraenoic acid; NK, natural killer.

17*S*-docosatriene called neuroprotectin D1 through epoxidation process (Hong et al., 2003). DHA is a poor substrate for COX. However, DHA can be converted to 17*R*-hydroxyDHA by aspirin-treated COX-2 and subsequently, to 17*R*-resolvin D series by 5-LOX (Serhan et al., 2002).

IV. PHYSIOLOGICAL ACTIONS OF EICOSANOIDS

The eicosanoids exert diverse actions on the cardiovascular, reproductive, respiratory, renal, endocrine, skin, nervous, and immune systems (Table 28.1). Many of the actions are due to their capacity to change vascular tone and cAMP concentrations in the tissues. The kinds of eicosanoids synthesized vary with the type of tissue. As an example, thromboxane A_2 (TXA_2), which is a potent platelet-aggregating agent, is mainly synthesized in platelets (Hamberg et al., 1975), whereas prostaglandin I_2 (PGI_2), which is a potent inhibitor of platelet aggregation, is formed by endothelial cells (Bunting et al., 1976). Eicosanoids are synthesized when and where cells are stimulated. Eicosanoids are not stored in cells, and they are rapidly metabolized. Thus, the effects of eicosanoids are locally expressed.

A. Prostaglandins and Thromboxanes

Prostanoids, PGs, and TXA_2 are produced by the action of COX, or PGHS (prostaglandin G/H synthase). The series 2 PGs and thromboxanes derived from arachidonic acid generally promote inflammation with potent chemotactic activity, serve as vasoconstrictors, and stimulate platelet aggregation. In contrast, the "3-series" PGs and thromboxanes from EPA act as vasodilators and antiaggregators. Prostanoids act as autacoids by activating specific G-protein coupled receptors (GPCRs). Prostacyclin, the IP; $PGF_{2\alpha}$, the FP; TXA_2, the TP; PGE_2, EP1-4; PGD_2, DP1, and DP2; EP2, EP4, IP, and DP1 are the relaxant receptors that increase cAMP levels, whereas EP1, FP, and TP are the contractile receptors that increase intracellular calcium levels. EP3 increases intracellular calcium, but decreases cAMP level.

TXA_2 is a potent vasoconstrictor and platelet agonist. TXA_2 is produced by platelet COX-1 and macrophage COX-2. The protective effect of aspirin on cardiovascular system is considered to be attributed to the inhibition of platelet COX-1. PGI_2 is a potent vasodilator and inhibitor of platelet aggregation. Increase of PGI_2 production suppresses the proliferation and migration of vascular smooth muscle cells in response to injury. PGD_2 is the major product released from mast cells during allergic responses and asthma. PGE_2 is involved in a variety of biological processes including cell growth and proliferation, contraction and dilation of smooth muscle, reproduction, and inflammation. There are four PGE_2 receptors, EP1–4. The differential expression of four receptors and PGE_2 level dictate the outcome of PGE_2 action in the specific cell type. EP4 activation leads to platelet inhibition at low-PGE_2 concentration while high concentration of PGE_2 activates EP3 resulting in platelet aggregation. $PGF_{2\alpha}$ induces smooth muscle contraction. The activation of FP is known to lead to vaso- and bronchoconstriction and cell proliferation. TXA_3 is much less potent than TXA_2 in inducing platelet aggregation (Needleman et al., 1979). However, PGI_3 is as effective as PGI_2 in inhibiting platelet aggregation. For this reason, dietary EPA is implicated to reduce the risk of thrombosis.

B. Leukotrienes

4-Series leukotrienes are generated from arachidonic acid by 5-LOX in leukocytes. Leukotriene A_4 (LTA_4) is an unstable intermediate that is metabolized to leukotriene B_4 (LTB_4). LTB_4 increases the adhesion of leukocytes and the recruitment of $CD8^+$ cytotoxic T lymphocytes at sites of inflammation. LTA_4 is also converted to LTC_4, LTD_4, and LTE_4 that are slow-reacting substances of anaphylaxis and promote endothelial cell permeability and airway smooth-muscle constriction during anaphylactic reactions. LTB_4 activates BLT_1 and BLT_2 while LTC_4, LTD_4, and LTE_4 activate $CysLT_1$ or $CysLT_2$ to exert proinflammatory activities (Funk, 2005).

LTB_5 that is generated from EPA is less potent than LTB_4 in chemotactic and aggregating activities for human neutrophils (Lee et al., 1984, 1985). However, the efficacy of 5-series leukotrienes compared with that of 4-series leukotrienes on other physiological responses is not known.

C. Lipoxins

5*S*,6*R*,15*S*-trihydroxy-7,9,13-*trans*-11-*cis*-eicosatetraenoic acid (LXA_4) and its positional isomer 5*S*,14*R*,15*S*-trihydroxy-6,10,12-*trans*-8-*cis*-eicosatetraenoic acid (LXB_4) are the major lipoxins found in mammals. The 15-epi-lipoxins are endogenous 15*R*-enantiomers of LXA_4 and LXB_4 and also called as the aspirin-triggered lipoxins. Lipoxins can be generated from arachidonic acid through three different enzymatic pathways. First, arachidonic acid is converted to LTA_4 by 5-LOX in polymorphonuclear leukocytes (PMNs). LTA_4 is subsequently metabolized to LXA_4 and LXB_4 by platelet 12-LOX. Second, arachidonic acid is also a substrate of 15-LOX to generate 15*S*-HPETE that is subsequently converted to 5,6-epoxytetraene by 5-LOX in PMNs. Then LXA_4 and LXB_4 are generated by epoxide hydrolases in leukocytes. Third, 15-epi-LXA_4 and 15-epi-LXB_4 can be generated by 5-LOX in leukocytes from 15*R*-HETE that is converted from arachidonic acid by aspirin-acetylated COX-2. Lipoxins are known to be expressed during the resolution phase of inflammation. Lipoxins are anti-inflammatory mediators that inhibit leukocyte migration, NF-κB activation, and the expression of chemokines, cytokines, and adhesion molecules (Gilroy et al., 2004). Lipoxin A_4 (LXA_4) activates two receptors, a G-protein-coupled receptor, LXAR (or FPRL1, formylpeptide receptor-like 1), and a nuclear receptor, AhR (Devchand et al., 2003; Maddox et al., 1997; Schaldach et al., 1999). LXA_4 decreases LTB_4- and fMLP-induced Ca^{2+} mobilization in PMNs resulting in the suppression of neutrophil chemotaxis, adhesion, and superoxide generation. LXA_4 stimulates clearance and phagocytosis of apoptotic PMNs, which is associated with increased production of TGF-β1 and decreased release of IL-8 and monocyte chemotactic protein-1 (MCP-1). A recent report has shown that the stimulation of denderitic cells with lipoxins resulted in the expression of suppressor of cytokine signaling (SOCS)-2 (Machado et al., 2006).

D. Resolvins

Whereas arachidonic acid is metabolized to epi-lipoxins by consecutive action of aspirin-aceylated COX-2 and LOX, resolvins can be generated from n-3 PUFAs, DHA, and EPA by COX-2 and LOX. Aspirin-acetylated COX-2 in vascular endothelial cells and LOX in leukocytes synthesize 18*R*-Resolvin E1 from EPA and 17*R*-Resolvin D series from DHA, respectively. 17*S*-Resolvin D series and protectin D1 are generated from DHA by LOX (Schwab and Serhan, 2006). The resolvins and protectins are endogenously found during the resolution phase of inflammation. The resolvins and protectins showed potent anti-inflammatory activities through the inhibitory effects on the leukocytes activation and the proinflammatory mediator synthesis (Serhan and Savill, 2005). Resolvin E1 showed the protective effect on inflammatory responses in periodontitis and 2,4, 6-trinitrobenzene sulfonic acid-induced colitis by decreasing PMN recruitment (Arita et al., 2005b; Hasturk et al., 2006). Resolvin E1 acts on a specific GPCR, ChemR23 to downregulate NF-κB activation (Arita et al., 2005a). Resolvin D series inhibits infiltration of leukocytes and IL-1β production in microglial cells (Hong et al., 2003). Both 17*S*-resolvin Ds and 17*R*-resolvin Ds have similar activity in inhibiting PMN infiltration. Protectin D1, 10,17*S*-docosatriene, possess potent neuroprotective activity by inhibiting NF-κB activation, COX-2 expression, and PMN infiltration in cultured neuronal cells and ischemic stroke animal model (Marcheselli et al., 2003).

Excessive and/or imbalanced synthesis of eicosanoids has been implicated in various pathological conditions, including thrombosis, inflammation, asthma, ulcers, and kidney disease. Specific inhibitors of enzymes in COX and LOX pathways and receptor antagonists for specific eicosanoids have been tried and used as therapeutic agents for many of the disorders mentioned above. Accumulated evidence suggests that the amounts and types of eicosanoids synthesized in tissues can also be modulated by manipulating dietary fatty acids. Thus, it may be possible that risk factors of certain chronic diseases can be reduced by modulating eicosanoid biosynthesis through changes in the composition of dietary fatty acids.

V. REGULATION OF EICOSANOID BIOSYNTHESIS

There are many factors that can regulate eicosanoid biosynthesis in tissues. First, substrate availability is an important limiting factor in the biosynthesis of eicosanoids. The immediate substrate for eicosanoid biosynthesis is free arachidonic acid (Lands and Samuelsson, 1968). Arachidonic acid is incorporated into tissue phospholipids. Cellular concentration of free arachidonic acid is extremely low. Thus, arachidonic acid has to be released by the action of phospholipases to initiate the synthesis of eicosanoids.

Second, pharmacological agents, which can inhibit activities of phospholipases or key enzymes in the arachidomic acid cascade, suppress the formation of eicosanoids. Corticosteroid and mepacrine, which inhibit phospholipase A_2, can inhibit release of the immediate precursor acids of eicosanoids (Flower et al., 1989; Hirata, 1989). Thus, they can suppress the formation of both COX- and LOX-derived eicosanoids. Many nonsteroidal anti-inflammatory drugs inhibit COX, resulting in preferential suppression of the formation of eicosanoids derived from the COX pathway (Nelson, 1989). COX requires peroxides, particularly lipid hydroperoxides, as activators (Lands et al., 1984). Thus, agents that affect peroxide levels would modulate the COX activity. Phenolic antioxidants are known to inhibit PG synthesis as a result of reduced lipid peroxide levels. Glutathione peroxidase also suppresses PG biosynthesis by removing lipid hydroperoxides (Lands et al., 1977).

The studies (Raz et al., 1988; Wu et al., 1988) indicate that the synthesis of COX enzyme itself is another important factor affecting PG biosynthesis. COX is irreversibly inactivated by the substrate (Hemler and Lands, 1980). This may be due to the oxidizing equivalent released during the reduction of PGG_2 to PGH_2 by PGH synthase, an enzyme that possesses both COX and peroxidase activity (Gale and Egan, 1984). If purified enzyme is incubated with the substrate, oxygen consumption ceases before the substrate is depleted. The reaction can be started again only if the fresh enzyme

is added. This suggests that the synthesis of new enzyme would be required to maintain the biosynthesis of PGs in tissues.

VI. MODULATION OF EICOSANOID BIOSYNTHESIS BY DIFFERENT DIETARY FATTY ACIDS

The immediate precursor acid of eicosanoids is nonesterified free fatty acid (Lands and Samuelsson, 1968). Since most PUFAs are esterified mainly in the *sn*-2 position of phospholipids, the amounts of precursor acid released from phospholipids can limit the rate and amounts of eicosanoid synthesis. The amounts and types of precursor acid released from phospholipids depend on the composition of fatty acids in tissue phospholipids, which in turn is influenced by the composition of dietary fatty acids.

There are two steps in which dietary fatty acids can modulate eicosanoid biosynthesis from arachidonic acid. The first step is in the desaturation and elongation. There is a competitive inhibition among linoleic acid and linolenic acid families for the conversion of the fatty acids to longer-chain PUFAs. The observation that n-3 PUFAs can decrease the conversion of linoleic acid to arachidonic acid was first made by Machlin (1962) and subsequently by Mohrhauer and Holman (1963).

Although these observations were made even before the discovery that PGs are synthesized from 20:3n-6 and arachidonic acid derived from EFAs, they provided a predictable basis for the modulation of eicosanoid biosynthesis by modifying dietary fatty acid composition. The far-reaching nutritional significance of this is that modification of the composition of dietary fatty acids can be used to modulate the biosynthesis of eicosanoids and consequent physiological responses. Furthermore, it can be used as a new strategy to prevent and/or ameliorate certain chronic diseases for which modulation of eicosanoid biosynthesis is desirable.

The second step in which dietary fatty acids can modulate the biosynthesis of eicosanoids is at the formation of endoperoxide intermediate. The n-3 fatty acids competitively inhibit the oxygenation of arachidonic acid by COX (Lands et al., 1973). The competitive inhibition between n-3 and n-6 PUFAs for desaturases and COX suggests that increasing n-3 PUFAs in diets would reduce arachidonic acid levels in tissue lipids and, consequently, would decrease the formation of eicosanoids derived from arachidonic acid. It has been suggested that the bleeding tendency and low incidence of coronary heart disease among native Greenland Eskimos, whose diets consist mainly of cold water marine animals, is attributed to enhanced levels of n-3 PUFAs in their blood lipids (Dyerberg and Bang, 1979; Dyerberg et al., 1978).

It has been shown that α-linolenic acid can suppress arachidonic acid levels in tissue lipids and eicosanoid biosynthesis from arachidonic acid, although it is less effective than longer-chain n-3 PUFAs, which are abundant in marine lipids (Hwang et al., 1988). α-Linolenic acid is not a substrate for COX or 5-LOX; thus, no thromboxanes or leukotrienes can be formed from it.

In addition to competitive inhibitory effects, another mechanism through which PUFAs reduce eicosanoid biosynthesis has been recently proposed. The expression of COX-2, which is a rate-limiting enzyme to generate PGs from arachidonic acid released from plasma membrane, is upregulated in response to proinflammatory stimuli. The activation of Toll-like receptors in response to microbial infection or endogenous agonists leads to enhanced expression of inflammatory gene products including COX-2 and cytokines (Beutler, 2004; Lee et al., 2001, 2003). Various PUFAs (n-6 and n-3) suppress the expression of COX-2 induced by bacterial components mediated through the inhibition of Toll-like receptor activation (Lee et al., 2001, 2003). n-3 PUFAs (EPA and DHA) showed the highest potency in inhibiting the activation of Toll-like receptors 2 and 4 resulting in the reduced PGE_2 synthesis (Lee et al., 2003, 2004). This provides a novel mechanism as to how dietary PUFAs regulate the level of eicosanoids at inflammatory sites.

If inclusion of n-3 PUFAs in diets is desirable to suppress eicosanoid synthesis, an important practical question would be how much of them should be added into the diet. It has been shown that when rats were fed graded amounts of n-3 fatty acids (trilinolein and fish oil) in the presence of a

constant amount of linoleic acid, the levels of arachidonic acid in tissue lipids and the formation of eicosanoids derived from arachidonic acid were suppressed in a dose-dependent fashion (Hwang et al., 1988). However, if rats were fed graded amounts of the n-3 fatty acids with constant ratios of n-3/n-6 fatty acids (0.62 for linolenate and 0.3 for menhaden oil groups) by concomitant increases in n-6 fatty acid, then there was no dose response within groups fed different levels of the same dietary fat at a constant n-3/n-6 ratio (Boudreau et al., 1991). These results indicate that the ratio of n-3/n-6 fatty acids in the diet, rather than the absolute amount of n-3 fatty acids, is the determining factor in inhibiting eicosanoid biosynthesis from arachidonic acid. Thus, in assessing desirable levels of dietary n-3 fatty acids, not only the absolute amounts of n-3 fatty acids but also the amounts of dietary n-6 fatty acids may have to be adjusted.

However, the results from human studies demonstrated that absolute amounts of fish oil, and not the relative amounts of fish and vegetable oil (ratios of n-3 and n-6 PUFAs), determined the magnitude of the reduction of arachidonic acid and increase in eicosapentaenoic in phospholipids of plasma and platelets (Hwang et al., 1997). The suppression of plasma triglycerides by fish oil was also not affected by varying amounts of dietary n-6 PUFAs (Hwang et al., 1997).

VII. INCORPORATION OF N-3 FATTY ACIDS INTO FOOD SYSTEMS

If incorporation of n-3 fatty acids into processed foods is desired in the future, plant oils containing α-linolenic acid as a major PUFA would have certain advantages over fish oil. α-Linolenic acid is abundant in certain plant seed oils, and it is the major PUFA in chloroplast lipids, as shown in Table 28.2. In spite of the suggested beneficial effect of n-3 PUFAs in reducing certain risks of coronary heart disease, there would be a limitation for the direct incorporation of fish oil into food systems owing to its undesirable flavor and the greater susceptibility of EPA and DHA to autoxidation compared to α-linolenic acid.

Fish oil or plant seed oils containing α-linolenic acid can be added as supplements to feeds for poultry or aquacultured fish to increase the n-3/n-6 fatty acid ratios. Feeding linseed oil or menhaden oil at the 1.0%, 2.5%, or 5.0% level to broiler chickens resulted in a significant increase in n-3 PUFAs and a decrease in n-6 PUFAs, with a consequent increase in the n-3/n-6 fatty acid ratio in thigh muscle lipids compared to the control group, which was fed a corn oil diet (Chanmugam et al., 1992). The increase in the n-3/n-6 fatty acid ratio by linseed oil was much greater than by menhaden oil.

It has been demonstrated that the lipids from pond-reared prawn and catfish have considerably lower amounts of n-3 fatty acids compared with lipids of their wild counterparts (Chanmugam et al., 1986). This difference is due to the diet used for commercial aquaculture, which contains soybean meal in which n-6 PUFAs predominate, whereas marine animals consume diets derived from plankton, which are rich in n-3 fatty acids. The content of n-3 fatty acid in aquacultured fish

TABLE 28.2
Fatty Acid Composition of Total Lipids from Selected Vegetables and Nuts (wt. %)

Fatty Acid	Frozen Spinach	Green Bell Pepper	Green Cabbage	Broccoli	Romaine Lettuce	Walnut	Linseed Oil
16:0	16.22	23.79	16.42	18.90	12.75	2.05	7.33
16:1n-7	3.82	0.09	3.66	2.72	3.76	8.45	—
18:0	0.99	9.54	2.87	2.70	1.27	1.81	3.48
18:1n-9	3.41	2.36	5.81	5.14	1.01	15.74	24.15
18:2n-6	13.97	47.91	25.24	18.13	13.51	55.80	16.97
18:3n-3	61.57	16.31	45.99	52.37	67.70	16.14	48.28
n-3/n-6 ratio	4.41	0.34	1.81	2.89	5.01	0.29	2.84

can also be increased by supplementing their feeds with fish oil or plant oil containing a high level of α-linolenic acid.

VIII. DIETARY γ-LINOLENIC ACID (18:3n-6)

Certain plant oils such as primrose seed and borage seed oil contain considerable amounts of γ-linolenic acid. Approximately 8% of the total fatty acids of primrose oil is 18:3n-6. Some studies suggested that primrose oil suppresses acute and chronic inflammation in rats (Kunkel et al., 1988; Tate et al., 1988). It was speculated that this anti-inflammatory effect of primrose oil is due to accumulation of dihomo-γ-linolenic acid (20:3n-6) derived from γ-linolenic acid, and dihomo-γ-linolenic acid competes with arachidonic acid for COX, resulting in suppressing the formation of diene PGs derived from arachidonic acid. Furthermore, dihomo-γ-linolenic acid cannot be converted to leukotrienes. However, dihomo-γ-linolenic acid does not normally accumulate in animal tissues in significant amounts. Dietary γ-linolenic acid would be converted mostly to arachidonic acid. The ratio of dihomo-γ-linolenic acid (20:3n-6) to arachidonic acid (20:4n-6) is normally less than 1:30 in rat tissue lipids. In fact, one of the studies (Tate et al., 1988) suggesting the beneficial effect of primrose oil on acute inflammation showed that arachidonic acid levels in serum lipids of rats fed primrose oil were much higher than those of rats fed chow or a safflower oil diet. Some studies (Kernoff et al., 1977) also suggested that the oral administration of dihomo-γ-linolenic acid is beneficial in the treatment of thromboembolic diseases. This suggestion may be based on the fact that, unlike PGE_2, PGE_1 derived from dihomo-γ-linolenic acid inhibits platelet aggregation. However, since dihomo-γ-linolenic acid can be converted to TXA_1 but cannot be converted to prostacyclin, the beneficial effects of long-term administration of dihomo-γ-linolenic acid are questionable. Furthermore, dihomo-γ-linolenic acid can be readily converted to arachidonic acid in tissues.

IX. DIETARY *TRANS* FATTY ACIDS

Geometrical and positional isomers of octadecenoate (18:1) comprise the major portion of fatty acid isomers present in partially hydrogenated vegetable oil. Various positional isomers of *trans*-octadecenoate can be desaturated *in vitro* by Δ9, Δ6, or Δ5 desaturases (Mahfouz et al., 1980). Some of them may be further elongated to longer-chain PUFAs (Kameda et al., 1980). However, the presence of 20-carbon PUFAs derived from *trans*-octadecenoate in significant amounts in tissue lipids has not been reported. Possible effects of geometrical and positional isomers of octadecenoate and longer-chain PUFAs derived from the isomers on eicosanoid formation have not been reported.

Three different kinds of geometrical isomers of linoleic acid are present in hydrogenated vegetable oil: 9-*trans*-, 12-*trans*-; 9-*trans*; 12-*cis*; and 9-*cis*, 12-*trans*-linoleic acid. 9-*cis*, 12-*trans*-linoleic acid is present in most vegetable shortenings in much greater quantities than 9-*trans*, 12-*trans*-linoleic acid (Lanza and Slovar, 1981). Unlike 9-*trans*, 12-*trans*-linoleic acid, 9-*cis*, 12-*trans*-linoleic acid can be converted to arachidonic acid containing a *trans* double bond (Privett et al., 1967). It was shown that *trans* isomers of arachidonic acid inhibited the formation of PGs from all-*cis*-20:4n-6 (Nugteren, 1970). Some *trans* isomers (9-*trans*, 12-*cis* and 9-*trans*, 12-*trans*) of linoleate inhibit the conversion of *cis*-linoleate to arachidonic acid (Privett and Blank, 1964; Privett et al., 1977). It was demonstrated that dietary *trans* (9-*trans*, 12-*trans*)-linoleate at levels equal to or greater than that of *cis*-linoleate suppresses arachidonic acid levels in tissue lipids and the formation of eicosanoid by platelets in rats (Hwang and Kinsella, 1979; Hwang et al., 1982). However, the level of 9-*trans*, 12-*trans*-linoleate does not exceed 0.5% of total fatty acids of partially hydrogenated vegetable oils (Lanza and Slovar, 1981). Such a level does not appear to be enough to suppress the formation of eicosanoids derived from arachidonic acid.

X. CONCLUSION

The level of intake of dietary PUFA recommended by the American Heart Association is based on the lowering effect of dietary PUFA on the blood cholesterol level, which is one of the important risk factors of coronary heart disease, the leading cause of death in the United States. Dietary PUFA has been used as an entity without differentiating the kind of PUFA. There are two types of dietary PUFA: n-3 and n-6 fatty acids. Linoleic acid (18:2n-6) is the predominant PUFA in the major vegetable oils consumed in the United States. Thus, linoleic acid is the major dietary PUFA in the diet. Among n-3 PUFA, α-linolenic acid (18:3n-3) is abundant in certain plant seed oils and is the major PUFA in chloroplast lipids. Longer-chain n-3 PUFAs such as EPA (20:5n-3) and DHA (22:6n-3) are abundant in marine lipids.

Twenty-carbon PUFAs derived from EFA are precursors of eicosanoids with diverse pathophysiological actions in the cardiovascular system and inflammatory processes. It has been implied that excessive and/or imbalanced synthesis of eicosanoids in tissues can lead to the development of certain pathological conditions. It is now well documented that the amounts and types of eiocosanoids synthesized in tissues can be modulated by manipulating the composition of dietary fatty acids. Epidemiological, clinical, and biochemical studies performed during the past two decades suggest that replacing dietary n-6 PUFA with n-3 PUFA to some extent is beneficial in reducing risks of certain chronic diseases. It has been revealed that dietary n-3 PUFA suppresses tissue levels of arachidonic acid, the biosynthesis of eicosanoids derived from arachidonic acid and the expression of inflammatory gene products including COX-2. Furthermore, eicosanoids derived from EPA possess a different potency with respect to various cellular responses as compared with those derived from arachidonic acid. This suggests that biosynthesis of eicosanoids and their cellular responses can be modulated by modifying the relative amounts of n-3 and n-6 PUFA in the diet. For this reason, types of PUFA may have to be defined in recommendations of dietary PUFA levels in the future dietary guidelines.

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